

EFFECTS OF ADVERSE EARLY-LIFE EVENTS ON AGGRESSION AND ANTI-SOCIAL BEHAVIOURS IN ANIMALS AND HUMANS

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Abstract

We review here the impact of early adversities on the development of violence and antisocial behaviour in humans, and present three etiological animal models of escalated rodent aggression, each disentangling the consequences of one particular adverse early-life factor. The review of the human data and those obtained with the animal models of maternal separation, post-weaning social isolation and peripubertal clearly show that adverse developmental conditions strongly affect aggressive behaviour displayed in adulthood, the emotional responses to social challenges and the neuronal mechanisms activated by conflict. While similarities between models are evident, important differences were also noticed demonstrating that the behavioural, emotional and neuronal consequences of early adversities are to a large extent dependent on etiological factors. These findings support recent theories on human aggression, which suggest that particular developmental trajectories lead to specific forms of brain dysfunctions and aggressive behaviour. However, dissecting the roles of particular etiological factors in humans is difficult, as these occur in various combinations; in addition, the neuroscientific tools employed in humans still lack the depth of analysis of those used in animal research. We suggest that the analytical approach of the rodent models presented here may be successfully used to develop integrative models of the complex relationship between early adversity, brain development and aggressive behaviour.

Introduction

Current explanations for the development of violence and antisocial behaviour emphasize the importance of early factors, which in conjunction with genetic predispositions have a large role in shaping behaviours displayed in adulthood (Craig, 2007; Moffitt, 2005; Slutske, 2001). While neuroscientific evidence clearly shows that early life events have a strong impact on brain development, eventually modifying the subsequent behavioural phenotype (Caspi et al., 2002; McGowan et al., 2009; McCrory et al., 2011), the interaction between early adversities, brain development and behaviour are still poorly understood. Although recent advances in brain imaging techniques opened an important new window for understanding the neural underpinnings of aggressive behaviour (Anderson and Kiehl, 2012), animal models remain valuable tools in disentangling and dissecting the contribution of particular neurobiological factors, as they are devoid of the human cultural influences.

Several animal models have been developed to capture cardinal features of early adversity-induced aggression in humans and to study the underlying endocrine, neuronal, genetic and epigenetic mechanisms. These models are centred on stressors delivered during critical periods of early life, e.g. the period of maternal care, weaning and puberty. The relevance of these models for aggression research was greatly enhanced by the recent introduction of new behavioural techniques, which detached from the classical approach of studying natural aggressiveness by mimicking etiological factors of aggression-related psychopathologies and by identifying deviant forms of aggression that arise as a consequence of these treatments. Deviant features include mismatches between provocation and response (e.g., when aggression strongly exceeds species-typical levels), disregard of species-specific rules (e.g., aggression towards juveniles, females, or directed towards vulnerable body parts, when male opponents are attacked), and insensitivity towards social signals by opponents (e.g., submissive opponents are attacked) (Haller and Kruk, 2006; Miczek et al., 2013). Behaviours fulfilling these criteria are perceived as deviations from the "natural rules" that govern aggression in animals, and resemble important aspects of aggression-related psychopathologies.

We strongly believe that the control of aggression cannot be understood without integrating animal findings of translational value and human findings. Close interactions between the two sides offers human research the chance to take advantage of the depth of analysis allowed by the advanced neuroanatomical and neurofunctional methodologies currently used in animal research, while research on animal aggression will greatly benefit from incorporating information on the phenomenon it models. Therefore, we review here early developmental factors that engender aggression in humans and present three developmental models of rodent abnormal aggression which model specific early etiological factors of aggression: repeated maternal separation (RMS), post-weaning social isolation, and peripubertal stressors. The presentation of models follows the same structure to easy their comparison. Firstly, the construct validity of each model is examined under the heading "The concept". These sections are followed by the presentation of abnormal behavioural features, the emotional background of aggressive behaviours displayed, and their neural background.

Early life factors contributing to antisocial behaviour in humans

While the prevalence rates of antisocial behaviour, conduct problems and general aggression in human populations are well documented (Kazdin, 1995; Ford, 2008), understanding of the mechanisms that underlie individual differences in adolescent and early adult antisocial behaviour remains relatively embryonic. Theoretical explanations offered to account for the transmission of these influences and associated interactive processes fall into two primary domains: (1) intergenerational transmission hypotheses, and (2) family socialization hypotheses. Advocates of an intergenerational transmission perspective emphasize the importance of early susceptibility factors (genetic predisposition, prenatal and early postnatal environmental influences and their epigenetic manifestation) as a point of origin in understanding the expression and development of psychopathology in children, adolescents and adults (Connell & Goodman, 2002). Advocates of a family socialization perspective emphasize the importance of contextual influences, such as harsh parenting practices, as antecedents of later antisocial behaviour (Patterson, 1982; Stover et al., 2012). Common to both intergenerational transmission and family socialization perspectives is the increasing application of a process-oriented

perspective, such that emphasis is placed on the identification of mediating and moderating processes underlying specific early risks and the onset and development of later antisocial behaviour problems.

Early manifestations of antisocial behaviour in humans

There is now substantial evidence that precursors to psychiatric problems like conduct disorder oppositional defiant behaviour/disorder, and attention deficit hyperactivity disorder (ADHD) are evident in children as young as 2 or 3 years of age (Caspi et al., 1996; Shaw et al., 2000). In order to understand the development of psychiatric symptoms in adolescence and early adulthood it is necessary to identify the temperamental characteristics in children that are associated with later behaviour problems or psychiatric disorder. In general, specific early child temperamental characteristics can indicate elevated risk for the development of later disruptive behaviour problems. This is most evident for children 3 years old and older, although some studies have found effects for children as young as 2 years. The temperamental precursors to externalizing disorders include an inability to inhibit behavioural responses to stimuli (behavioural disinhibition), fearlessness, and high negative reactivity or emotionality (Nigg, 2006; Shaw et al., 2003). A handful of studies have followed children from early childhood in an effort to characterize trajectories of behaviour problems. These studies have found evidence for consistency in disruptive behaviour problems from early to middle childhood and adolescence with increased predictive ability when the earliest ages of assessment are 3 rather than 2 years (Mesman et al., 2001; Shaw et al., 2000). Detailed reviews of the literature on early prediction of later disruptive behaviour have reported that to date there are only modest links between infancy and adolescent behaviours (Campbell et al., 2000). One difficulty in identifying children early for disruptive behaviours is that behaviours like aggression and other disruptive behaviours are common during early childhood, thus increasing the likelihood that children could be identified as at risk, but who then do not develop elevated symptoms later. Despite these concerns, children who develop psychiatric symptoms within the externalizing spectrum (aggressive behaviours through to antisocial behaviour disorder) appear to have identifiably different temperamental traits than children who do not develop such disorders and from children who develop psychiatric symptoms along the internalizing spectrum (anxiety, depression etc.).

Neuroendocrine processes underlying antisocial behaviour in humans

There are clear indications that a fundamental feature of the early brain in response to chronic and severe stress exposure is dysregulated neurobiological functioning (VanGoozen et al., 2007). In human studies, cortisol secretion is typically studied in relation to HPA axis activation, and heart rate and skin conductance responses are used as markers of autonomic activity. The HPA axis is a stress mobilization system that varies in tonic activation over the course of the day (i.e., peak in the morning followed by decline) and plays a key role in mounting a response to physical and psychological stressors (Sapolsky et al., 2000). Typically measured through circulating cortisol levels, basal HPA activity that is either too high or too low may signal problems. As described by the Adaptive Calibration Model of stress system development, HPA activation may adapt upward or downward to manage sustained adversity, each of which comes with costs to physical and psychosocial functioning (Del Giudice et al., 2011; Laurent et al., 2013). Studies of antisocial adults have observed a negative relationship between cortisol levels and behavioural dysregulation (Bergman & Brismar, 1994). Hypotheses proposed for this inverse association suggest that such individuals may be physiologically under-aroused, that the negative feedback mechanisms acting on the HPA axis are hypersensitive, or that they have an increased threshold for stress (VanGoozen et al., 2008). Few studies have been conducted on cortisol levels or the cortisol response to stress in aggressive children, and there have been equivocal findings across studies. Some studies have found associations between reduced basal cortisol

concentrations and aggressive behaviour (VanGoozen et al., 2004), other studies found no such relationship (Azar et al., 2004), with others noting a positive relationship (Van Bokhoven et al., 2005). An important caveat to these studies is differences in the measurement of cortisol activation that may underlie differences in the pattern of association with antisocial behaviours reported.

A core limitation of past research examining neurobiological processes underlying the development of antisocial behaviour in humans is that the vast majority of findings derived from human studies have been generated from correlational research designs, thereby precluding causal inferences relating to the role of cortisol activation underlying human aggression. There have been very few studies with a design capable of showing that low cortisol levels indeed precede the onset of antisocial or aggressive behaviour throughout adolescence and into young adulthood. An exception to this dearth of evidence, and which highlights a longitudinal (albeit noncausal) link between low cortisol levels and aggressive behaviour, is that of Shoal et al., (2003). Results from this study showed that low cortisol was moderately predictive of aggressive behaviour 5 years later and, further, that this relationship appeared to be mediated by the effects of cortisol on personality attributes marked by self-control deficiencies (Shoal et al., 2003). Another longitudinal study (McBurnett et al., 2000) showed that clinic-referred boys with consistently low cortisol levels in samples obtained 2 years apart evidenced the highest levels of aggression and conduct disorder symptoms over time. Studies focusing on parents and children suggest a degree of heritability in cortisol levels. For example, parent antisocial personality symptom counts have been shown to be inversely related to cortisol concentrations in children (Vanyukov et al., 1993). This suggests that cortisol may be involved in the intergenerational transmission of antisocial behaviour and provides further indirect evidence that this steroid plays a role in antisocial behaviour (VanGoozen et al., 2007).

Prenatal influences on antisocial behaviour in humans

Prenatal drug exposure has been shown to be associated with risk for antisocial behaviour. First, maternal smoking during pregnancy has been shown to increase risk of behavioural problems in exposed individuals. Specifically, it has been linked to increased conduct problems, including delinquency and aggression (Weissman et al., 1999; Gaysina et al., 2013) and with higher rates of inhibitory control problems, including ADHD and attention problems in children (Turner et al., 2011; Thapar et al., 2003). A number of studies also find effects of smoking during pregnancy on offspring conduct and related problems, including criminality (Boden et al., 2010; Wakschlag et al., 2011). Second, prenatal marijuana exposure has been related to learning, memory and impulsivity throughout childhood (Richardson et al., 2002), to increased delinquency and attention problems during middle childhood and adolescence (Day et al., 2011), to a greater likelihood to initiate smoking and marijuana use during adolescence (Porath et al., 2005), and to response inhibition in young adults (Smith et al., 2004). Third, prenatal cocaine exposure has been linked to deficits in arousal and attention regulation from infancy through middle childhood (Mayes et al., 1998; Fisher et al., 2011), to more hyperactive and fussy temperament and more behaviour problems throughout childhood (Richardson 1998; Chasnoff et al., 1998), and to cocaine use during adolescence (Delaney-Black et al., 2011). Despite these findings of positive associations between smoking during pregnancy and drug use with risk for antisocial behaviour, there is also evidence of null findings. For example, some studies have not found links between smoking during pregnancy and child problem behaviours or ADHD, after controlling for potential confounds (Ball et al., 2010; Biederman et al., 2009). One possible explanation for the mixed findings is that apparent prenatal exposure effects could be explained by genetic or by other environmental risk factors (D'Onofrio et al., 2008; Rice et al., 2009), as discussed further below.

Postnatal environmental influences on antisocial behaviour in humans

Two primary domains of the postnatal rearing environment have been shown to influence antisocial behaviour problems: parenting and inter-parental conflict, with negative extremes in each domain representing child maltreatment. Parental lack of sensitivity (McElwain et al., 2007; Yap et al., 2008), rejecting parenting (Shaw et al., 2005), maternal hostility (Little & Carter, 2005), and maternal control (Degnan et al., 2008) have each been associated with disruptive behaviours in early childhood — a known precursor to antisocial behaviour. Exposure to frequent, intense and poorly resolved inter-parental conflict makes unique contributions to later behaviour problems in children both directly and in interaction with children's emotional reactivity (Ingoldsby et al., 1999). Maltreatment has been associated with long-term changes in the neuroendocrine stress systems, specifically HPA axis dysregulation (Tarullo & Gunnar, 2006). Longitudinal evidence suggests that adults, who were maltreated as children, show basal cortisol and HPA axis dysregulation, when compared to non-maltreated controls (Heim & Nemeroff, 2001; Tarullo & Gunnar, 2006). Inter-parental conflict also predicts children's conduct problems, with associations due to genetic and nonshared environmental influences (Harden et al., 2007). Evidence also suggests that genetically-influenced aversive temperamental characteristics in childhood may also play a role in exacerbating the effects on the postnatal environment. For example, such behaviour might tax parents' patience and regulated attention. Aversive parental responses might, in turn, serve as antecedents of later externalizing problems, particularly when contextual supports are also lacking (Patterson, 1982; Shaw & Bell, 1993). Continuity in these reciprocal pathways to externalizing behaviour is moderate to strong beginning at age 2–3, extending through school age (Shaw et al., 2000, 2003) and early adulthood (Caspi et al., 1995, 1996). For example, by age 3, children rated as high in irritability, fearlessness, and emotional lability have been found to be three times more likely to meet criteria for DSM-III-R antisocial personality disorders at 18 and 21 years than 3-year-olds with normative scores on these dimensions (Caspi et al., 1995). However, there is clear evidence that psychosocial interventions that target parenting practices can reduce the risk for antisocial behaviour problems, even among highly delinquent populations (Henggler & Schoenwald, 2011).

Neuronal background

Numerous neuronal explanatory models of human abnormal aggression were developed over the last decades. Despite the large number of such attempts, no consensus was reached regarding the neuronal underpinnings of aggression-related psychopathologies. One group of models emphasizes the role of cognitive and emotional processes and identifies disrupted prefrontal and amygdala functioning as the neuronal substrates of this type of malfunctioning (Anderson et al., 1999; Davidson et al., 2000; Herpertz and Sass, 2000). Other models can be perceived as attempts to integrate higher order neural/psychological functions and lower order executive mechanisms e.g. those residing in the hypothalamus and central gray (Berdahl, 2010; Blair, 2010). Recently, an almost "purely" neural theory of human aggression was also developed (Potegal, 2012). The circuitries hypothesized to underlie abnormal forms of aggression are overall similar, but the models are discrepant regarding both the brain areas included in the circuitries and their particular roles. A subgroup of these theories suggests that the two major types of human aggression namely reactive and instrumental aggression result from different neuronal malfunctions, which derive from specific developmental trajectories (Berdahl, 2010; Blair, 2010; Lopez et al., 2004).

Importantly for the present review, the animal models presented below may successfully be used to reveal the interactions between developmental (i.e. genetic and environmental) factors, the types of aggression resulting from these and the particularities of underlying neuronal mechanisms.

Caveats in the study of human aggression and antisocial behaviour

A significant limitation of past research in the study of the family-based origins of aggression and antisocial behaviour is a predominant reliance on biologically related parents and offspring. In biological families, associations between parent and child characteristics may result from an underlying shared genetic characteristic that simultaneously influences both the trait in the parent and the trait in the child. Precisely because these shared genes influence the behaviours of both parent and child, it is not possible to unambiguously disentangle, whether parent-to-child influences are a result of shared genetic effects, family environmental influences, or both. While the interplay between genetic and environmental factors has historically been examined using twin-based research designs, twin studies assume that monozygotic (from the same fertilised ovum) and dizygotic (from two separately fertilised ova) twin pairs share environment to the same extent, so a greater degree of concordance in monozygotic pairs is attributed to genetic factors. However, it has been shown that the environments children experience may vary distinctly even when children are genetically identical. Recent studies using adoption-based research designs have advanced insights in this area of study and are showing specificity of parent and family level influences on children's antisocial behaviour problems (Harold et al., 2011; Harold et al., 2013). Understanding the interplay between genetic, prenatal, neurobiological and postnatal factors on the etiology of anti-social behaviour remains an area of continued scientific, practice and policy relevance. In a case study of conduct disorders in the UK, it was estimated that preventing conduct disorders in the most disturbed children would save around £150,000 of life time costs per case (£5.25 billion). Extension of this figure to international impact rates makes a substantial case for continued investment in the promotion of understanding relating to the causes, mechanisms and potential intervention sites aimed at remediating human antisocial behaviour.

Early life factors contributing to social dysfunctions in rodents

The concept

As outlined above, children who experienced early social and emotional neglect (i.e. lack of tight bonds with their care takers, often summarized as poor parenting) or even abuse are at higher risk to develop social dysfunctions including high levels of aggressive behaviour, inappropriate social responses and psychopathologies with early onset (Susman, 2006; Kim and Cicchetti, 2010; Kotch et al., 2008; Woodruff and Lee, 2011). Based on this established link between early life trauma and juvenile, pubertal and adult antisocial behaviour problems in humans, animal models are needed to reveal the underlying neurobiological principles, which fulfil the criteria of face, construct and predictive validity.

Here, we will discuss 3 established rodent models of adverse early life experiences, i.e. the paradigms of repeated maternal separation (RMS), post-weaning social isolation and peripubertal stress which have been successfully employed to study mechanisms of social dysfunctions, in particular of increased intermale aggression.

The animal model of maternal separation

One of the best characterized rodent models of early adverse life experiences, mirroring adverse human childhood experiences such as emotional neglect and social deprivation is the separation of pups from their mother. There exist various paradigms of maternal separation for rats and mice including (i) a single separation of the litter from

the dam for 24 h within the first week of life (Lehmann et al 2002; Levine 2000; Schmidt et al 2004), (ii) a daily repeated separation of the whole litter from the dam for up to 3 hrs during the first 2 weeks of life (here called repeated maternal separation; RMS) (Plotsky et al 1993; Wigger & Neumann, 1999), and (iii) early social deprivation of the pups by separating them from both the dam and the litter mates for several hours per day (Pryce et al 2003; Ruedi-Bettschen et al 2006). RMS as a rodent model for early social life stress has been shown to fulfil the criteria of face, construct and predictive validity. Therefore, it is not surprising that it has been extensively used to study long-term consequences not only on social behaviours, but also on emotionality, cognitive functions, stress coping strategies, and associated neuroendocrine and neuronal adaptations. Also, RMS has been used to study the epigenetic underpinnings of these behavioural alterations lasting into adulthood (Murgatroyd et al. 2004).

Impact of RMS on aggressiveness

RMS has been used to investigate early life stress-induced alterations in various social behaviours including play-fight behaviour (social play) and intermale aggression in juvenile, adolescent and adult male rats or mice. Social play is seen in most species and a prerequisite for the development of adequate adult social behaviours (Meaney and Stewart, 1979; Panksepp et al., 1984; Vanderschuren et al., 1997). The behavioural patterns displayed by rat juveniles, such as nape attacks, pinning and supine postures, are related to adult social, aggressive and sexual behaviour, but differ substantially from adult behaviours with respect to intensity, quality and contextual settings (Pellis and Pellis, 1998). As expected, juvenile rats show the highest level of social play, whereas we found a sharp decline in the duration and frequency of play-fight behaviour at adolescence; whereas it was almost invisible in adult male rats (Veenema and Neumann, 2009). Exposure of rat pups to RMS significantly affected the development of social play compared with non-separated controls. Specifically, male juvenile and adolescent RMS offspring spent less time with playful social interactions, but showed a higher frequency of nape contacts towards the unknown age-matched play partner at age of 5 weeks. Moreover, juvenile RMS rats showed more vigorous fur pulling and less supine postures towards the play partner. As the total duration of play-fight did not differ between RMS and control rats during the 10-min test session, RMS may not affect spontaneous social play motivation, but rather shifted the specific elements of social play into a more dominant, rougher and more aggressive direction. The lower number of supine postures in juvenile RMS rats further suggests that RMS rats avoid submissive postures. Taken together, the behavioural patterns seen in juvenile offspring exposed to early life stress by RMS can be interpreted as inappropriate social play behaviour including rather aggressive elements.

The effects of RMS experience on social behaviour continue into adulthood as RMS rats generally displayed a higher level of aggressive behaviour, when confronted with a male intruder in their home cage during a 10-min RI test (Veenema et al 2006). The excessive aggression of RMS rats was specifically reflected by the display of lateral threat, offensive upright and keep down. However, the open question remains as to whether adult RMS rats also display more abnormal aggressive behaviour, which hasn't been studied so far. Also, species-specific consequences of RMS on adult aggression seem to exist. Despite the similar RMS-induced increase in anxiety- (plus-maze) and/or

depression- (forced swim test) related behaviours in both Wistar rats and C57Bl/6 mice, RMS induced a decrease in adult intermale aggression in mice reflected by longer attack latencies (Veenema et al 2007). In support, RMS exposure was recently shown to suppress male aggression in peripubertal C57Bl/6J mice, and this was accompanied by reduced plasma testosterone, reduced AVP and increased OXT hypothalamic immunoreactivity (Tsuda et al. 2011).

Impact of RMS on emotionality

RMS is an established rodent model for anxiety- and depression-related diseases, as it results in increased anxiety levels, passive stress coping, for example in the forced swim test reflecting behavioural despair or depression-related behaviour, decreased exploration of a novel environment, and increased acoustic startle responses, (Wigger and Neumann, 1999; Veenema *et al.*, 2006; Caldji *et al.*, 2000; Aisa *et al.*, 2007; Huot *et al.*, 2002; Kalinichev *et al.*, 2002; Romeo *et al.*, 2003). Antidepressant treatment was shown to partly reverse these behavioural consequences (Huot et al 2002; MacQueen et al 2003). Also, RMS-exposed mice show a higher vulnerability to chronic psychosocial stress in adulthood with respect to emotional, physiological and immunological stress parameters (Veenema *et al.*, 2008). Thus, in a chronic psychosocial stress model of chronic subordinate colony housing, the most severe stress-effects were seen in those mice, which had been exposed to adverse early life experiences such as RMS. As we found a lower level of aggression associated with a more passive stress-coping style in adult RMS mice, it is most likely that adult RMS mice of that study tended to be more submissive during exposure to the dominant male mouse during the chronic psychosocial stress exposure with the consequence of more severe stress effects. The effects of RMS on emotional and neuroendocrine parameters seem to be sex-dependent, as male rats were found to be more vulnerable to RMS compared with female rats (Wigger and Neumann 1999). Also, the individual genetic background, for example with respect to trait anxiety, importantly determines the severity of RMS effects on emotionality (Neumann *et al.*, 2006).

Neuronal background

The above mentioned behavioural alterations induced by RMS are accompanied by alterations in various neurotransmitter, neuropeptide and hormonal systems. For example, an increased (re)activity of the HPA axis reflected by elevated mRNA expression of corticotrophin releasing hormone (CRH) in the hypothalamic paraventricular nucleus (PVN), and increased plasma adrenocorticotropin (ACTH) and corticosterone concentrations in response to an acute stressor (Plotsky & Meaney, 1993; Wigger & Neumann, 1999; Huot *et al.*, 2002; Gardner et al 2005) (Veenema et al. 2009) were found mostly studied in adult RMS rats. Also, after postnatal stress juvenile rats have elevated, i.e. adult-like levels of basal plasma corticosterone compared with juvenile control rats. Thus, the increase in plasma corticosterone observed during a single separation period (de Kloet *et al.*, 1996; Schmidt *et al.*, 2004) seems to be extended throughout the juvenile period and is likely to impact on brain development, including the maturation of social and emotional behaviours. Accordingly, the elevated corticosterone levels might be causally related to the increase in offensive social play observed in male juveniles exposed to RMS similar to the observation that circulating corticosterone determines adult intermale aggression (Haller *et al.*, 2000b; Haller *et al.*, 2000a; Haller *et al.* 2004;

Kruk et al., 2004; Mikics et al., 2004; Veenema et al., 2006). For example, an acute rise in plasma corticosterone promotes aggression via fast and, thus, non-genomic effects (Mikics et al., 2004), and may contribute to the escalation of violent behaviour under stressful conditions (Kruk et al., 2004). However, monitoring of ACTH and corticosterone responses to an aggressive encounter or a non-social stimulus is still needed in RMS juveniles; although the elevated ACTH response to forced swimming in adult RMS rats indeed indicates changes in the HPA axis regulation as a result of RMS.

In addition to HPA axis alterations, RMS-induced changes were also described for neuropeptidergic systems such as the arginine vasopressin (AVP) and oxytocin (OXT) systems. Both AVP and OXT are key players in the regulation of a wide variety of social behaviours, including intermale and maternal aggression, affiliation, sexual behaviours and social cognition (Neumann, 2009; Lukas and Neumann 2013; Donaldson and Young, Calcagnoli et al. 2013; Goodson, 2008). The expression of their receptors, i.e. the V_{1A} -R and OXT-R, develops in a brain region-specific manner from juvenile over adolescence into adulthood (Lukas et al., 2010; Tribollet et al., 1991) suggesting their particular role in the maturation of social behaviours. Exposure to RMS severely interfered with these developmental adaptations, which is likely to underlie the alterations in aggressive behaviours after RMS exposure observed. For example, exposure to RMS increased V_{1A} -R binding in the piriform cortex in adolescent and adult rats and in the lateral septum in juveniles, and decreased OXT-R binding in the agranular cortex (juveniles and adolescents), the lateral septum (adults) and the ventromedial hypothalamus (adults) (Lukas et al 2010).

In addition to the AVP and OXT receptors, differences in local gene expression, immunoreactivity and release patterns of the neuropeptide AVP have also been associated with differences in adult intermale aggression (for review see Compaan et al., 1993; Everts *et al.*, 1997; Veenema and Neumann 2007; Neumann et al. 2010). With respect to early life stress, the increase in aggressive play-fight behaviour and in adult aggressive behaviour in RMS rats was accompanied by a significant higher AVP mRNA expression and AVP immunoreactivity in hypothalamic areas such as the PVN, SON and lateral hypothalamus. In adult rats, this increase was not seen under basal conditions, but a more pronounced rise in hypothalamic AVP expression was found in RMS rats in response to exposure to the RI test compared with non-separated control rats (Veenema et al., 2006; Veenema and Neumann 2009). Unexpectedly, a similar increase in AVP mRNA expression in the PVN was also found in adult male RMS mice despite the fact that they showed less aggression (Veenema et al 2007). This points towards the possibility of a primary effects of RMS on anxiety, which may in turn modulate aggression in a species-specific manner (Beiderbeck et al., 2012). The long-lasting rise in basal AVP expression found in adult RMS rats was found to be due to epigenetic modulation of the AVP gene (Murgatroyd et al. 2004).

In extension of its many pro-social effects, OXT has recently been described to exert anti-aggressive effects in male (Calcagnoli et al., 2013) and female (DeJong et al., under revision) rats. Also, the OXT system is sensitive to adverse early life experiences as described above, but whether the RMS-induced increase in intermale aggression is indeed accompanied by alterations in brain OXT neurotransmission or directly related to changes in local OXT-R binding needs to be shown. The human findings of a negative correlation between basal plasma or CSF OXT levels, and aggression and childhood

traumatisation (Heim and Nemeroff 2001) further suggest a dysregulation in the OXT system caused by early life stress.

The 5-HT system also significantly contributes to the regulation of aggressive behaviours and is sensitive to early life stress (Delville *et al.*, 1998; Lesch 2011). In this context, an interaction effect between childhood environment and 5-HT transporter genotype on violent behaviour was found (Bennett *et al* 2002; Reif *et al* 2007). In agreement with the general view that 5-HT exerts an inhibitory control over impulsive aggression (Olivier & Mos, 1990; Ferris & Delville, 1994; Ferris, 1996; Ferris *et al.*, 1997), we found a reduced 5-HT immunoreactivity in the anterior hypothalamus in RMS-treated rats suggesting a decrease in local 5-HT release associated with increased aggression (Veenema *et al* 2006). Further, a negative correlation was revealed between 5-HT immunoreactive staining, e.g. in the anterior hypothalamus, and the duration of lateral threat in RMS rats (Veenema *et al* 2006). Thus, as a balanced activity of the 5-HT system within the anterior hypothalamus seems to be critical for the development of appropriate aggressive behaviour, RMS-induced alterations in the activity of the 5-HT system are likely to contribute to the elevated levels of intermale aggression seen after exposure to RMS.

Conclusions

The rodent model of RMS has been proven to be a suitable paradigm to reveal the effects of early life neglect on juvenile and adult intermale aggression and the underlying neurobiological mechanisms. Exposure to RMS resulted in a more aggressive play-fight behaviour in juvenile and increased intermale aggression in adult rats and was shown to be accompanied by alterations in the AVP and 5HT systems. Whether RMS also induces alterations in the quality of aggression and a shift towards abnormal aggression needs to be shown. Also, provided a suitable behavioural test for female (non-maternal) aggression is employed such as the female intruder test (FIT; DeJong *et al.*, in revision) the RMS paradigm seems suitable to study sex-specific differences in RMS-induced alterations in juvenile or adult aggression.

The animal model of post-weaning social isolation

The concept

Scientific interest in early social relationships was prompted by the seminal studies of Harlow (1965) who showed that the social isolation of monkeys in early life "obliterates the animals socially" and results in a sequence of symptoms that resemble those seen in children who experience poor parenting, social exclusion and loneliness. These early developmental conditions emerged as predictors and worsening factors of externalizing problems and are believed to significantly contribute to the expression of emotionally laden (reactive) aggressive behaviour from childhood into adulthood (Chapple *et al.*, 2005; Fite *et al.*, 2013; Kim and Cicchetti, 2010; Nesdale and Duffy, 2011).

Post-weaning social isolation models this condition by eliminating social contacts with peers from weaning into early adulthood. Rodents submitted to this paradigm show strong signs of social incompetence as adults (diminished ability to integrate in groups, Harlow *et al.*, 1965; Tulogdi *et al.*, 2012), and display quantitative and qualitative changes in aggressive behaviour that are in many respects similar to those induced by

early social neglect in children (Day et al., 1982; Toth et al., 2008). Taken together, these considerations demonstrate the construct validity of the model.

Impact of post-weaning social isolation on aggressiveness

Effects on aggression were best described in male rats reared in isolation after weaning (postnatal day, PND 21) to PND 80. When faced with opponents in their home-cage, such rats show enhanced levels of aggression as evidenced by increased number of bites delivered to opponents (Toth et al., 2008). This feature may not be considered abnormal *per se* as differences from controls are not particularly dramatic (Haller, 2013). In addition to quantitative changes, however, a series of qualitative behavioural changes also develop. Rats reared in isolation preferentially target their bites onto vulnerable body parts of opponents (head, throat and belly). Unusual attack targeting is associated with marked deficits in attack signaling by offensive threats. Moreover, the two features appear correlated: the more bites are delivered to vulnerable targets the less likely are these preceded by social signals (Toth et al., 2008). Thus, post-weaning social isolation leads to the emergence of dangerous forms of attack, which are poorly predictable for opponents due to deficient social signaling. Abnormal attacks are associated with other features indicative of disrupted behaviour. In contrast to controls, socially isolated rats show strong signs of behavioural agitation evidenced by rapid switches from one behaviour to another; moreover, their high aggressiveness is associated with increased defensiveness, which is a prominent feature of emotionally laden aggressive behaviours deriving from early social neglect (Toth et al., 2008). Changes in aggressiveness develop rather rapidly in rats, as shown by increased play fighting after just 4 weeks of post-weaning social isolation (i.e. around PND 50) (Wall et al., 2012).

The impact of isolation rearing on aggression was less well characterized in other species. In mice, this condition increased the duration of offensive threats (Workman et al. 2011); in another study, mice isolated from weaning attacked opponents in neutral arenas, a behaviour that was absent in controls (Bibancos et al., 2007). Thus, mice reared in isolation displayed aggression in a context where this behaviour is not normally expressed, which may be considered an abnormal feature. In gerbils, post-weaning social isolation increased both offense and defense, which replicates the behavioural ambiguity (parallel increases in offense and defense) seen in rats (Shimozuru et al., 2008). Taken together, these studies suggest that post-weaning social isolation results in abnormal forms of aggression in rats and several other rodent species.

Noteworthy, disrupted behaviour appears highly persistent. Exposing isolation-reared rats to three encounters over 6 days (PND 80-86) did not result in significant behavioural changes over time (Toth et al., 2011). Moreover, abnormal attack features persisted after 3 weeks of re-socialization (*social isolation*: PND 21-80; *aggression-testing*: PND 80; *re-socialization*: PND 80-101; *re-testing for aggression*: PND 104; Tulogdi et al., 2012).

Impact of post-weaning social isolation on emotionality and stress responsiveness

Basal glucocorticoid levels and heart rates were evaluated at multiple time-points after weaning in isolation-reared rats and no differences from controls were noticed (Toth et al., 2011; Shimozuru et al., 2008; Workman et al., 2011). By contrast, acute autonomic and glucocorticoid responses to aggressive encounters markedly increased (Toth et al.,

2011). As Weiss et al. (2004) did not show comparable effects with non-social stressors, we recently studied rats in the open-field, elevated plus-maze, social interaction, and RI tests (Mikics et al. in preparation). Non-social tests did not, while social tests did increase glucocorticoid levels over those seen in controls, suggesting that rats isolated from weaning are particularly sensitive to social stressors. Similar findings were obtained in humans, where early social neglect-related HPA-axis dysregulation was most evident in social contexts (Fries et al., 2008; Pesonen et al., 2010).

Neuronal background

To evaluate the neural background of abnormal aggression shown by rats reared in isolation, first we investigated brain c-Fos expression profiles in rats exposed to the RI test (Toth et al., 2012). Brain areas normally involved in the control of territorial aggression (BNST, medial and lateral amygdala, and the mediobasal hypothalamus) and stress-related structures (PVN, locus coeruleus) were over-activated as compared to controls. These findings are in line with theories on the neural control of human reactive aggression that is highly emotional and is believed to result from the over-activation of the amygdala and mediobasal hypothalamus (Blair, 2010). Interestingly, however, the prefrontal cortex –generally believed to limit aggressive behaviour– was also over-activated by post-weaning social isolation. This unusual finding prompted a second study that specifically focused on the prefrontal cortex (Biro et al., in preparation). Rats reared in isolation showed reduced prefrontal volumes and reduced glia counts. Interestingly, these deficits were restricted to the right-hand side of the prefrontal cortex similar to highly aggressive humans; moreover, the magnitude of change (10-15%) was also similar (Yang and Raine, 2009). Still, the prefrontal cortex was markedly over-activated by aggression in isolation-reared rats. These paradoxical findings mirror those obtained in humans submitted to simulated aggressive conflicts that resulted in reactive forms of aggression. Under such conditions, the activation of the prefrontal cortex and the level of aggressiveness showed a positive correlation (Lotze et al., 2007; Montag et al., 2012; New et al., 2009; Strenziok et al., 2011; Veit et al., 2010). Thus, post-weaning social isolation-induced abnormal aggression is associated with chronic deficits in prefrontal functioning but enhanced acute responses to aggression in this brain area.

Conclusions

Post-weaning social isolation is followed by profoundly altered patterns of aggression, characterized by natural rule-breaking (e.g. attacks on vulnerable targets and poor social communication), offensive ambiguity (parallel increases in offense and defense), and behavioural agitation in adulthood. Alterations in behaviour are associated with enhanced physiological responses to social stressors, deficits in prefrontal development, and the over-activation of brain areas that acutely control aggressiveness. The behavioural/emotional/neuronal profile of rodents submitted to this model resembles that seen in human reactive aggression, which –most notably– often results from early social neglect. As such, the model appears a useful tool to study the developmental aspects of human reactive aggression.

The animal model of peripubertal stress

The concept

There is abundant evidence indicating that exposure to stress during childhood and puberty – termed hereafter peripubertal period– is associated with an increased risk to develop a broad number of psychiatric disorders (Heim and Nemeroff, 2001; Watt et al., 2009). The development of pathological aggression is particularly observed following peripubertal adversity, especially when involving fear and maltreatment (Jonson-Reid et al., 2010).

Given the profound hormonal and neurodevelopmental changes occurring around puberty, the brain is during this period highly susceptible to environmental perturbations, such as stress exposure (Paus et al., 2008; Blakemore, 2012). Early rodent studies indicated that stress exposure during puberty increases agonistic behaviours during adolescence (Sachser, 1993; Delville et al., 2003). However, stress in these studies was induced through confrontations with other conspecific animals, therefore precluding the exclusion of social learning as a critical factor in the development of pathological aggression. Recently, a rat protocol based on exposure to fear-inducing experiences (predator odor and exposure to an elevated platform) during the peripubertal period (on scattered days during the period comprising postnatal days P28 to P42), and excluding social learning factors, has been shown to be a valid model for pathological aggression – including intimate partner violence– with face, construct and predictive validity (Cordero et al., 2012; Marquez et al., 2013). This peripubertal stress rat model of pathological aggression leads to enhanced aggression not only in males (Cordero et al., 2012; Marquez et al., 2013) but also in peripubertally stressed female rats (Cordero et al., 2013). The following subsections will specifically deal with the characterization and implications of this model.

Impact of peripubertal stress on aggressiveness

Male rats submitted to fearful experiences during peripuberty exhibit an overall pattern of pathological aggression (Marquez et al., 2012; Cordero et al., 2013; Poirier et al., 2013) according to the criteria summarized in the Introduction. These findings fit with human studies showing that children exposed to stress show increased risk to develop subsequent aggressive behaviour (Reif et al., 2007; Weder et al., 2009). Increased aggression towards a male conspecific, as evaluated in the RI test, was also found when, instead of stress, animals were injected with a stress dose of corticosterone (5 mg/kg, daily) on the same days when animals are stressed in the peripuberty stress protocol (Veenit et al., 2013). Remarkably, in addition to their more aggressive behavioural pattern at adulthood, animals treated with corticosterone at puberty already displayed increased play fighting during adolescence, suggesting that the enduring effects observed might be the consequence of more immediate effects in social behaviours potentially affecting the neurodevelopmental trajectory of corticosterone-treated animals (Veenit et al., 2013).

Interestingly, females are also susceptible to increased programming of aggressive behaviour by peripuberty stress (Cordero et al., 2013). Peripuberty stressed females show increased aggression toward females, both during diestrus and estrus, as well as towards a male partner during their first encounter. These females also show increased maternal aggression against a male intruder. These findings fit with human reports showing that the probability to develop personality disorders accompanied by aggression is increased

by exposure to adverse experiences during childhood, not only in boys, but also in girls (Johnson et al., 1999; Foy et al., 2012).

Impact of peripubertal stress on emotionality

In addition to leading to pathological aggression, exposure to peripubertal stress in rats has, as well, a profound impact in different aspects of emotionality. Intriguingly, the effects are paradoxically different when examined during late adolescence and at adulthood. At adolescence (studied during P45-P51), peripuberty stress leads to decreased anxiety-like behaviour –evaluated in the elevated plus maze and open field– both in males and females (Toledo-Rodriguez and Sandi, 2011), which is in contrast with the increased anxiety-like behaviour displayed by these animals at adulthood (Marquez et al., 2013). In addition, during late adolescence, peripuberty stressed animals show increased risk-taking and novelty-seeking behaviours (Toledo-Rodriguez and Sandi, 2011). However, and at difference to what is found at adulthood (Marquez et al., 2013), peripuberty stressed rats do not show symptoms of depressive-like behaviour (measured at the forced-swim test) nor changes in the corticosterone response to stress when evaluated at adolescence.

At adulthood, in addition to the enhanced signs of aggression, anxiety- and depression-like behaviours indicated above, peripuberty stressed male rats exhibit reduced sociability, as indicated by their reduced exploration of a juvenile conspecific in the three-chambered test (Marquez et al., 2013). This pattern of behavioural changes is reminiscent of findings in humans exposed to traumatic stress during equivalent developmental periods (i.e., childhood and puberty) (Heim et al., 2010). In humans, depression and enhanced aggression are frequently comorbid, particularly during adolescence and early adulthood, and both have been associated with early life stress (Patterson et al., 1991; Beach et al., 2010). Importantly, when the same stress protocol used during peripuberty is applied at adulthood, no behavioural effects (in aggression or emotionality) are observed, which strongly supports the view that peripuberty is a period of special sensitivity to the behavioural programming of aggressive and emotional behaviours by stress (Marquez et al., 2013).

At the hormonal level, peripuberty stress was found to lead to a reduced corticosterone response towards the end of the stress protocol (Marquez et al., 2013), an effect also observed in response to mild stress in adult animals treated with corticosterone during the peripuberty period (Veenit et al., 2013). This data fits with studies in humans showing that stress exposure during peripuberty is associated with lower cortisol in adulthood (Hamilton et al., 2008). Blunted cortisol responses have been frequently found in posttraumatic stress disorder patients (Resnick et al., 1995; Yehuda et al., 1996), and progressive attenuation of cortisol across age was reported in victims of childhood sexual abuse (Trickett et al., 2010). Moreover, peripuberty stress in rats was also found to lead to an increased plasma testosterone/corticosterone ratio measured after the resident-intruder test (Marquez et al., 2013), resembling human data in violent individuals (Terburg et al., 2009).

Neuronal background

Peripuberty stress in rats leads to changes in the activity of corticolimbic circuits that can be already observed during the late adolescence period following stress

exposure. More precisely, these adolescent rats show increased metabolic rates in hippocampus, basal amygdala and cingulate cortices when exposed to fear cues (Toledo-Rodriguez et al., 2012). At adulthood, enhanced activity in the amygdala is still observed, while a blunted response of the medial orbitofrontal cortex is evidenced immediately after the resident-intruder test (Marquez et al., 2013). This pattern of brain activity is reminiscent of findings of amygdala hyper-functioning and medial orbitofrontal cortex hypo-functioning in humans with impulsive aggression (Raine et al., 1997, 1998).

In addition, peripuberty stressed males showed enhanced expression of the monoamine oxidase A (MAOA) gene in the prefrontal cortex, while treatment with a MAOA inhibitor prevented the emergence of pathological aggression (Marquez et al., 2013). MAOA gene variants have been found to increase the risk of antisocial and aggressive behaviours following childhood adversity (Caspi et al., 2002; Reif et al., 2007; Weder et al., 2009). However, subsequent work showed that extreme levels of early life stress can lead to increased aggression independently of MAOA or other 5HT-related genetic variations (notably, the 5HT transporter) (Reif et al., 2007; Weder et al., 2009). Strikingly, the observed changes in brain activity in peripuberty stressed rats are similar to neuroimaging observations in humans presenting the MAOA allelic variant that is associated with an enhanced risk for impulsive-aggressive behaviour (Davidson et al., 2000; Meyer-Lindenberg et al., 2006). Altogether, these data put forward the key role of neurobiological factors elicited by peripubertal adverse experiences for the emergence of violent behaviours.

Conclusions

Exposure of rats to fear-inducing, stressful experiences during the peripubertal period is a recently developed animal model for pathological aggression with face, construct and predictive validity (Cordero et al., 2012; Marquez et al., 2013). Face validity relates to the heightened attacks exhibited by peripuberty stressed male rats against non-threatening conspecific individuals and, particularly, by their persistent attacks even when opponents display defensive behaviour, as this pattern resembles key features in human impulsive aggression. Construct validity is supported by the reproduction of some of the key alterations in brain functioning observed in aggressive-impulsive human individuals (i.e., changes in the amygdala–medial orbitofrontal cortex circuitry (Coccaro et al., 2007, 2011), increases in the testosterone/corticosterone ratio (Terburg et al., 2009) and alterations in the serotonergic system (Buckholtz and Meyer-Lindenberg, 2008). Predictive validity is provided by the effectiveness of the treatment with a MAOA inhibitor in reducing aggression, as also found in humans. Therefore, this animal model of peripubertal stress-induced adult aggression represents a valuable opportunity for the study of the neurobiological mechanisms sustaining violent behaviours, as well as for the development of novel therapeutic treatments.

Overall Conclusions

The human findings and laboratory models reviewed here converge in the view that aggression-related problems appear to result from developmental factors. In a broader perspective, causative mechanisms are also similarly found in clinical and preclinical data. Genetic factors (Natarajan et al., 2009; de Boer et al., 2003), drug exposures (Melloni and Ricci, 2010; Jackson et al., 2005), hormonal influences, and social

conditions are identified as main modulators of brain development and aggressive behaviour in both animals and humans (Fig. 1) (Blair et al., 2010, Potegal, 2012). There is, however, a fundamental difference between abnormal rodent aggression and escalated human aggression. Each animal model employs one single etiological factor and studies its consequences for behaviour, emotionality and brain function. In other words, animal models dissect etiological factors and study them separately. This is impossible in humans, where various etiological factors almost always occur in combinations; those who are neglected as children may also be exposed to stressors in puberty; moreover, they are at risk to use drugs at this age.

One of the conclusions that derive from animal models is that each etiological model affects behaviour, emotionality and brain functions in specific ways. For example, maternal separation did not affect attack counts, but increased the propensity for dominance; post-weaning social isolation increased the number of attacks, but made opponents defensive, while peripubertal stressors increased attack counts and dominance alike. The same applies to hormone production and brain function; both were affected in model-specific ways (see above). Taken together, these findings support the notion that there are several emotional/neurobiological "roads" to abnormal aggression, and these are etiological factor- and/or time-dependent. While the precise dissection of etiological factors is problematic in humans, there seems to be a considerable variability in the mechanisms that lead to escalated aggression in particular groups of people. One can hypothesize that this is due to the specific combination of etiological factors that resulted in escalated aggression; in other words, model-specific mechanisms in animals would translate into individual and/or group variability in humans.

The three rodent models reviewed here show considerable face and construct validity, and result in phenotypes that resemble human conditions in multiple ways. Consequently, their analytical (etiological factor-dissecting) nature may become both exploratory and explanatory for particular aspects of human aggression. The integrating (multiple factor-encompassing) nature of human studies may be exploited to understand the complexity of phenomena underlying escalated aggression. Analytical and integrating approaches fortunately complement each other in general, and their combined application may elevate the understanding of abnormal aggression at new levels. Results obtained so far directly or indirectly suggest that the idea of finding *one* particular mechanism for abnormal aggression should be abandoned; dissecting the roles and effects of individual etiological factors, and integrating these findings into complex models remains an important task for the future.

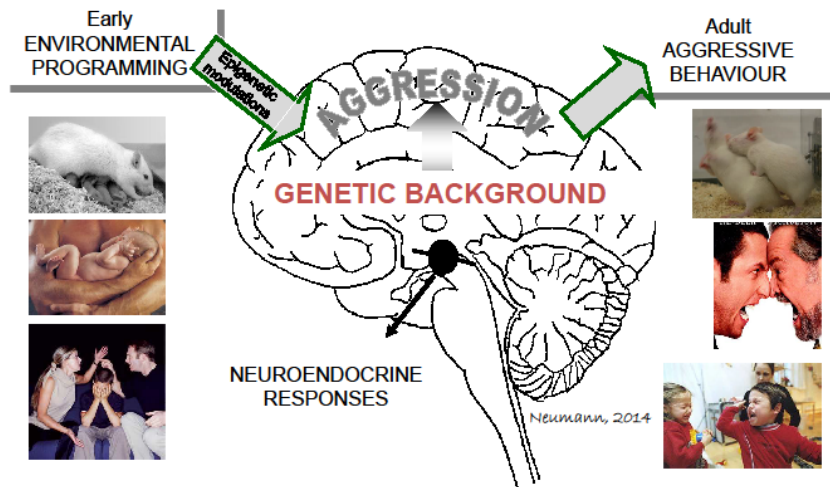


Fig 1

Schematic drawing of the effects of adverse early life experiences on juvenile, adolescent and adult aggressive or violent behaviours shaped by the individual genetic background and epigenetic processes, which modulate both behavior and neuroendocrine functions.

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